evident that the growth was destroyed, and only a large area of choroidal destruction marked the place where it had been. There was considerable fluctuation in the size of the mass between applications of radium. In 1924 the vision without correction was 6/12+. The child entered public school and kept near the head of her class until vision began to fail in the autumn of 1927, due to the development of posterior cortical cataract. On May 9, 1928, the anterior part of the lens was clear, but on the posterior capsule was a dense layer of granular substance more dense at the center. The large vessels of the fundus could be seen, but the details of the disc were obscured. In the inferior temporal quadrant was an irregular area 2 by 3 disc-diameters, which gave a white reflex. The area was not elevated, and although not clearly focused was apparently on the same level as the fundus. Large vessels were not seen in that region, and there were no other lesions present. Transillumination was now good. The tumor had been destroyed by the radium. The increasing cloudiness of the lens is characteristic of complicated cataract seen in eyes with extensive choroidal destruction and probably was not due to the direct action of radium.

A RETINOBLASTOMA IN A MAN AGED FORTY-EIGHT YEARS*

F. H. VERHOEFF, M.D.
Boston

The following case is reported because it is believed to be the only one of retinoblastoma† known to have occurred in an adult. It is also unusual, however, as regards the site of origin, mode of extension of the growth, and the abundance of rosettes in the latter. As the patient was not seen by me until after the removal of the eye, the clinical notes on the case are from the hospital records.

John W., white, aged forty-eight years, was admitted to the Infirmary August 27, 1928, on the service of Dr. Derby. He had

* From the Massachusetts Eye and Ear Infirmary.

† This term, suggested by me in 1924 as a suitable designation for the tumor commonly known as glioma retinæ, was adopted by the American Ophthalmological Society in 1926.

been married sixteen years, with no living children. His wife had one miscarriage, and one baby died soon after birth. Three sisters were alive and well. The general health of the patient was excellent, and he never had any serious illness. Six months ago he noticed spots like "snowflakes" before his left eye. One week ago he went to an optician for an examination and discovered that the sight of this eye was almost gone. He had no pain in the eye at any time, but had a feeling of numbness on the left side of the head.

Examination.—The right eye was normal, tension 10 mm. (Souter), V. = 20/20. The left eye was free from congestion, the cornea clear, and the anterior chamber of normal depth. The slit-lamp showed a moderate number of cells in the aqueous. The iris vessels were dilated. The pupil was 3.5 mm. wide, and reacted poorly. There were posterior synechiæ at 7 o'clock; the lens showed a posterior cortical cataract, and the vitreous was full of fine opacities. On the nasal side, far forward, there was a circumscribed separation of the retina. The projection was irregular in contour and its surface showed prominent blood-vessels. It transilluminated fairly well, but irregularly. The tension was 24 mm. (Souter). Vision equalled ability to count fingers at 2 feet.

A general physical examination was negative. The patient was well nourished. There was no enlargement of the pre-auricular or other glands.

Clinical Diagnosis.—Intra-ocular neoplasm, left eye.

On August 27, 1928, the left eye was enucleated under local anesthesia, and a glass ball implanted. He was discharged on September 3, 1928.

On March 29, 1929, there was no evidence in the orbit of recurrence of the tumor. His general health was excellent. The patient stated that about a week after the removal of his eye he began to have severe headaches on top of his head whenever he lay down. The headaches entirely ceased, however, about six weeks ago. The fundus of the right eye was normal. The color of the right iris was noted to be light brown, and the patient stated that both eyes were of the same color.

PATHOLOGIC EXAMINATION

Fixation in 10 per cent. formalin for forty-eight hours, and 70 per cent. alcohol containing 2.5 per cent. hydrochloric acid for twenty-four hours. Celloidin sections were stained in hematoxylin and eosin.

Macroscopic.—The globe was of normal size and shape, measuring 25 mm. anteroposteriorly and 24.5 mm. horizontally. In the upper nasal quadrant there was a large, grayish-white, intra-ocular tumor which extended from the root of the iris to a point 3 mm. from the optic disc, and from the vertical meridian above to slightly below the horizontal meridian. It was 10 mm. in its greatest thickness. The retina left the surface of the growth posteriorly and then was separated from the choroid by serum for a considerable distance.

Microscopic.—A section passing through the middle of the growth (fig. 1) showed that the anterior portion of the latter was situated within and greatly distended the ciliary body, anterior choroid, and suprachoroidal space. This was the largest part of the growth. The invasion reached as far forward as the canal of Schlemm and backward to within 2 mm. of the equator, where the growth abruptly elevated the surface of the choroid almost at right angles to the sclera. The inner layers of the choroid and ciliary body and the ciliary processes were relatively intact, and formed a covering for the tumor. There was, however, a gap 3.5 mm. wide, beginning 8 mm. from the filtration angle, where the uvea had been broken through by the tumor which here attained its greatest thickness. Through the gap the tumor extended forward over the inner surface of the ciliary body as far as the ciliary processes, and backward over the inner surface of the choroid, forming in each instance a mass about 1.25 mm. in thickness. The remainder of the tumor as seen in this median section consisted of two large nodules in contact with each other, one 4.5 mm. and the other 6.5 mm. in diameter. The larger nodule was separated from the anterior portion of the tumor by a small space filled with blood and serum. Over the surface of the smaller nodule the retina extended forward for about 2.25 mm. and then ended rather abruptly. A small isolated piece of retina was found near the choroid between the two nodules; otherwise the pars optica retinæ in this region had been completely destroyed by the tumor. Other sections showed these nodules connected together and continuous through the gap in the uvea with the anterior part of the tumor. Sections made through the upper and lower parts of the tumor showed the uveal surface here unbroken so that it was evident that the area of the gap must have been comparatively small.

The parenchyma of the tumor consisted almost exclusively of rosettes of various sizes (figs. 2 and 3), identical in appearance with

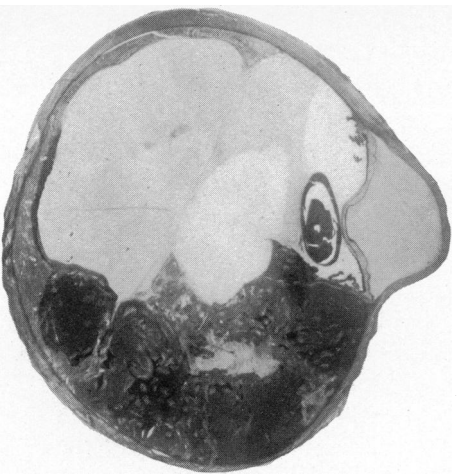

Fig. 1.—Photograph of section passing near middle of tumor, showing invasion of choroid and ciliary body, break in uvea, and involvement of retina.

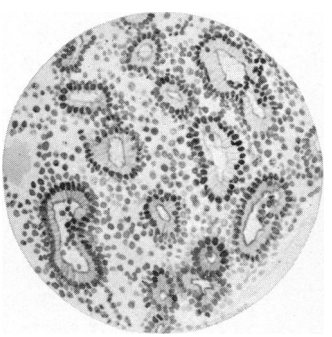

Fig. 2.—Showing rosettes. Zeiss obj. DD oc. 3.

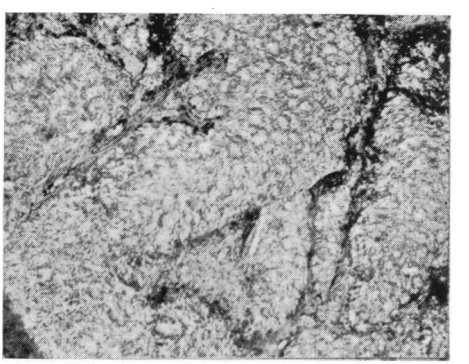

Fig. 3.—Photograph showing abundance of rosettes and trabeculæ composed of choroidal tissue.

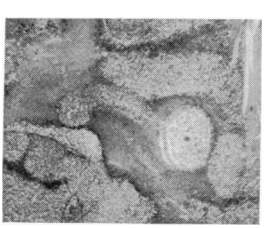

Fig. 4.—Photograph of area in tumor showing cylindric formations and surrounding necrosis.

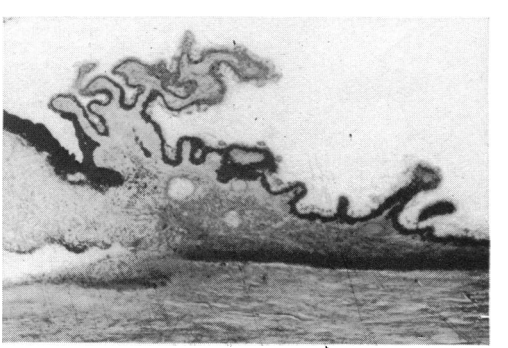

Fig. 5.—Photograph showing hyaline change in stroma of ciliary processes and proliferation of pars ciliaris retinæ.

those of a retinoblastoma. Bordering the lumen of each rosette was a membrane analogous to the external limiting membrane of the retina, but the cells did not project through this membrane. In sections stained in phosphotungstic acid hematoxylin there were seen, under favorable conditions, two dots (centrosomes) in the center of each cell at the level of the fenestrated membrane.*

Occasionally the appearance of a fairly long irregular tubule was produced, evidently due to the compression of a large rosette by the surrounding cells. Rows of cells representing parts of walls of rosettes were often seen. Many of these had obviously resulted from the invasion of rosettes by the neighboring cells. In some places there were small areas in which no definite rosettes could be recognized. Here the cytoplasm of the cells was scanty and stained faintly, and often the cells showed faintly stained processes, often bipolar. The nuclei were similar to those in the rosettes. They were usually round or oval, occasionally pear-shaped. Each nucleus showed a well-marked nuclear membrane with chromatin knobs attached to it. A single nucleolus could sometimes be recognized. Occasionally a cell with one very large nucleus, or with two or three large nuclei, was seen. Cells in mitosis were abundant throughout the tumor.

The stroma of the tumor was scanty, and in the anterior portion consisted chiefly of pigmented trabeculæ remaining from the invaded ciliary body and choroid. In the posterior portion it consisted of newly formed connective-tissue trabeculæ. There was no reticulum between the tumor cells. The blood-vessels were confined to the trabeculæ and all had definite walls. Within the tumor there were numerous areas of complete necrosis. These were entirely free from inflammatory cells, but many contained more or less extravasated blood. Some of them were being replaced by connective tissue. There were a number of large irregular spaces filled with delicate connective tissue infiltrated with serum that had evidently been produced in this way. One such space, 4.5 by 2 mm. in size, is shown in figure 1, extending up to the gap in the uvea, and another is shown near the sclera. Within the areas of necrosis there were frequently seen sharply defined circular areas of tumor cells, each area containing a central vessel, figure 4. These were really cylindric formations seen in cross-section, such as described and explained by Wintersteiner.[1]

* Such centrosomes were discovered by me in the rosettes of retinoblastoma in 1904.[3]

Microscopic examination of the other parts of the eye showed nothing of special importance, aside from changes confirming the age of the patient. There were no intra-ocular metastatic deposits from the tumor. The cornea and sclera were normal. The anterior stroma of the iris showed a degree of pigmentation corresponding to an iris of light brown color. The iris stroma showed many obliterated vessels and, in the region of the sphincter, many pigmented clump cells. In most sections the root of the iris blocked the filtration angle. The canal of Schlemm was distended with blood. The lens showed slight cataractous changes in the posterior cortex. In some sections the capsular epithelium had extended on the nasal side to the posterior pole. The ciliary processes were congested and their stroma showed the marked fibrous and, in some instances, the complete hyaline change with scanty and feebly staining nuclei characteristic of senile eyes (fig. 5). At the bases of the processes partly or wholly obliterated vessels were frequently seen. The unpigmented layer of the pars ciliaris retinæ, both over the ciliary body and pars plana, showed typical marked senile hyperplasia. These changes were present on the temporal side of the eye as well as elsewhere. There was marked cystoid degeneration of the pars optica and pars ciliaris retinæ in the region of the ora serrata. The macula was *in situ* and contained ganglion-cells in normal numbers. The retina elsewhere was separated more extensively than was apparent in the macroscopic examination, and where separated showed gliosis. The subretinal space contained serum and numerous masses composed of macrophages and giant-cells enclosing cholesterin, fatty acid crystals, and lipoids. Some masses of the same kind had been incorporated in the tumor. The pigment epithelium showed the usual proliferative changes occurring under such conditions. The choroid in the fundus showed slight perivascular infiltration with lymphocytes. Near the optic disc the membrane of Bruch showed the basophilic staining described by Verhoeff and Sisson.[4] The optic disc was not cupped. In the arachnoid sheath of the optic nerve a number of corpora aranacea were seen—sometimes two in one section.

COMMENTS

That this tumor was a retinoblastoma (so-called glioma retinæ) there can be no doubt. The rosettes, the bipolar cells, and the areas of necrosis made a picture never produced by a tumor of any other kind.

The unique feature of this case, as already stated, was the advanced age of the patient, forty-eight years. Since no case occurring in an adult has ever previously been recorded, a question may be raised as to whether or not the eye examined microscopically actually belonged to this patient. While there was no other reason to doubt that the bottle containing the eye was correctly labelled, the identity of the eye was established by the following facts:

(a) The clinical and pathologic examinations of the eye were in agreement; (b) no other eye containing a tumor was received during the period in question; (c) no child's eye was received or removed at this institution for a period of a month before or a month after the date of enucleation given on the bottle; (d) the eye was of adult size; (e) the eye microscopically showed changes characteristic of senile eyes, namely, fibrosis, hyaline change, and obliterated vessels in the stroma of the ciliary processes, marked senile proliferation of the ciliary epithelium, basophilic staining of Bruch's membrane in the choroid, and corpora aranacea in the arachnoid sheath of the optic nerve.

As a matter of fact, the changes in the ciliary processes were alone sufficient to prove that the eye was from a patient close to fifty years of age. Such changes are never seen in a child's eye even under pathologic conditions, and I failed to find them in a series of 70 eyes affected with retinoblastoma. The basophilic staining of Bruch's membrane was also alone sufficient to prove the age of the patient. Verhoeff and Sisson[4] found such staining to be due to a purely senile condition, unrelated to any pathologic process in the eye, and the youngest patient in which they observed it was forty-eight years of age.

In the 70 previous cases of retinoblastoma in which the eyes were examined microscopically at this institution by me, the youngest patient was aged ten weeks and the oldest seven years. In the 467 cases collected from the literature

by Wintersteiner,[1] 376 patients were under four years of age, only 10 patients were over nine years of age, and the oldest patient was aged sixteen years. Since Wintersteiner's publication, a remarkable case has been reported by Maghy.[2] The right eye was removed from a girl at the age of two years, examined microscopically and found to contain a glioma (retinoblastoma). At the age of twenty years the left eye became glaucomatous, was removed, examined microscopically, and found to be almost completely filled with a retinoblastoma. The tumor contained rosettes and had extended outside the globe. This seems to be the oldest patient having a retinoblastoma hitherto observed.

Recently two cases of supposed retinoblastoma in adults have been reported, one by Gerard and Detroy[5] in a woman aged sixty-six years, the other by Gerard and Morel[6] in a man aged thirty-five years. The pathologic report in each case was without illustrations and was so brief and inadequate as to be almost meaningless. In the first case a tumor the size of a pea was found in an eye shrunken as the result of an old inflammatory condition. The tumor was said to be composed of neurogliar cells and neurogliar fibrils and to contain pseudocysts. As a retinoblastoma never forms neurogliar fibrils, it is safe to say that the tumor in question differed in nature from the tumor commonly known as glioma retinæ. Possibly it was a mass of hyperplastic neuroglia such as not infrequently arises from separated retinas in shrunken eyes. In the other case, the retina was detached by a tumor, but the size and situation of the tumor were not stated. Here again the tumor was described as being composed of neuroglia and, therefore, it also could not have been a retinoblastoma. Possibly it was a non-malignant tumor such as described by Jonas S. Friedenwald.[7]

Aside from the age of the patient, the present case was unusual also in that the tumor, in proportion to its size, had invaded the uvea to a far greater extent than had any of the

numerous other neuroblastomas examined by me. In fact, the largest part of the tumor was within the ciliary body and anterior choroid. Wintersteiner did not describe such an invasion of the uvea in his series. The site of origin of the tumor was also unusual. While, of course, this could not be exactly determined, the shape and position of the tumor, and especially the place of rupture of the uvea, showed clearly that its origin was near the ora serrata. Wintersteiner found that in 63 cases from the literature in which the site of origin of the tumor could be approximately determined, this was in the region of the ora serrata in only 12 cases. Finally, the tumor was unusual in its extraordinary content of rosettes. I have previously seen tumors in which rosettes were as abundant in places, but few in which practically the entire tumor was composed of these structures.

The advanced age of the patient, the site of the tumor, and the abundance of rosettes in the latter raise the question as to whether or not its mode of origin may not have been different from that of the retinoblastoma of children. There seems to be no doubt that tumors in general are of two types. One type is definitely congenital in origin, or arises from some congenital "anlage," the other arises late in life from cells which have originally been normal. The epithelial tumors of the lacrimal or salivary glands are examples of the first, and epitheliomas of the skin, of the second type. Tumors of the first type, in spite of their congenital origin, often do not manifest themselves clinically until late in life. For this reason it seems possible that the present tumor was of the first type and hence essentially of the same origin as the retinoblastoma of children. If this were so, however, it would be expected that many other such cases would have occurred in adults. It seems to me, therefore, at least possible that this tumor was of the second type as regards its origin.

If we believe this to be true, it is reasonable to assume

further that the tumor arose from the unpigmented layer of the pars plana ciliaris retinæ, for this would best explain the abundance of rosettes, the extensive and evidently early invasion of the ciliary body, and the site where the invasion began. It is true that the only malignant tumors known to have arisen from the pars ciliaris retinæ have been of an entirely different nature—while they have formed rosettes of a certain type, they have also differentiated into normal retinal embryonic tissue, as I pointed out in 1904.[3] But these tumors have occurred only in children and have evidently been congenital in origin. On the other hand, hyperplasia of the pars ciliaris retinæ, including the pars plana, is common in senile eyes, and not infrequently gives rise to a small non-malignant tumor, often resembling an adenoma. Although, according to my own observations, the latter tumor always occurs in relation with a ciliary process, it seems possible that an area of senile hyperplasia in the pars plana might give rise to a malignant tumor such as occurred in the present case. It must be admitted, however, that further observations are necessary before a definite answer can be given to the question as to exact mode of origin of this tumor.

SUMMARY

This is believed to be the first case recorded in which a retinoblastoma has occurred in an adult. The tumor was observed both clinically and microscopically. The microscopic examination showed in the region of the ora serrata a large intra-ocular tumor indistinguishable from a retinoblastoma, extensively invading the retina, ciliary body, and choroid. The tumor consisted almost exclusively of rosettes. The possibility is suggested that it may have arisen from the pars plana ciliaris retinæ, and the question is discussed as to whether it arose from a congenital anlage or from an area of senile hyperplasia.

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5. Gerard et Detroy: Clin. opht., 1926, xxx, p. 328.
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DISCUSSION OF PAPERS OF DRS. BENEDICT AND VERHOEFF

DR. WARREN S. REESE, Philadelphia: Dr. Benedict's case is particularly interesting from the standpoint of heredity. About three years ago I was asked by Dr. Leavitt, a neurologist, to see a child with brain tumor. This child showed a receding choked disc. About a year previously a twin brother had died from brain tumor, the diagnosis of which was confirmed at autopsy. These twins went through almost exactly the same course of symptoms and signs and died within a year or two. As in the case of Dr. Benedict, they were identical twins. Unfortunately, an autopsy was not obtained in the twin I saw, but there was little doubt that these twins had exactly the same type of tumor in exactly the same situation.

DR. ADOLPH O. PFINGST, Louisville, Ky.: This Society is fortunate in that these two rare and interesting cases were presented at this session. I was especially interested in Dr. Verhoeff's case history, for up to now the report of a case of glioma in a patient of forty-eight years was unheard of. In fact, all of us have no doubt been accustomed to make tentative diagnoses of glioma from the age of the patient. This variety of neoplasm—the retinoblastoma of the Mallory classification—is strictly a disease of early life: one-third of the reported cases occurred in the first year of life and 80 per cent. of them in the first four years. Only 2 per cent. of the cases occurred after ten years, and as the essayist has told us, a few isolated cases have been reported in individuals beyond twelve years of age. I feel it is fortunate that this case in a man aged forty-eight years fell into the hands of Dr. Verhoeff, who is recognized as the outstanding ocular pathologist in this country, for his diagnosis will hardly be challenged, as might happen if one of us less versed in the microscopic study of pathologic tissue had made the report.

It seems to me that the abundance of Wintersteiner's rosettes observed and shown by Dr. Verhoeff are convincing. The same is

true of the banking of the cells with well-defined large nuclei around the blood-vessels appearing as tubes or rings in the section accordingly as the vessels were cut across or lengthwise. It was noted that the nuclei of these cells became more faint the farther away they were from the vessels and that they were not visible in the intercellular substance.

It is interesting to note that the location of Dr. Verhoeff's tumor was contrary to the rule, as it emanated from or near the ora serrata and not in the posterior quadrant of the eye, where four out of five gliomas have their origin.

In regard to Dr. Benedict's cases, I think that they are unique in their rarity, for the incident of homologous intra-ocular growths in twins has probably never occurred before. This report supports the belief that retinoblastomas emanate in some embryonic anomalies in the retina. The early appearance of these tumors, their frequent presence in several children of the same parents, and the fact that the disease often develops in multiple primary centers, all support the theory of Cohnheim regarding the genealogy of this variety of neoplasm.

Dr. Jonas S. Friedenwald, Baltimore: I would like to add one small bit of evidence in support of Dr. Verhoeff's conclusion that this was the eye of a patient in middle life. I have had the unusual opportunity of examining histologically between two and three hundred eyes of infants and young children, and in none of these have I seen corpora amylacea in the optic nerve sheath. The invasion of the choroid in this case is rather remarkable and warrants the assumption, I think, that the tumor arose either in the ciliary epithelium or very close to the ciliary body, or, as an alternative suggestion, that the tumor arose in the retina near an old chorioretinal scar. Without such a lesion it seems to me difficult to believe that the tumor would so early penetrate Descemet's membrane.

Dr. H. Maxwell Langdon, Philadelphia: Dr. Benedict's complication of cataract in the eye which he managed to save out of the four, and which he suggests possibly might be due to a choroidal upset in the eye, reminds me of two cases which I have seen where irradiation had been used for an orbital growth in children. One was in the series Dr. Pfahler reported before the Section of the American Medical Association in Chicago four or five years ago. The growth was resorbed and the eye remained normal for some

time and then developed secondary lenticular changes without choroidal disturbance. I did a Ziegler operation on the lens and it absorbed, showing no fundus change. I am not sure that Dr. Benedict is right in saying that the irradiation was not the cause of this lenticular change, as I think it very possible that where an eye is developing, the effect of irradiation on the lens may be sufficient to cause an opacity. In these cases I know that posterior changes had no effect because the posterior of the eye was normal.

DR. E. V. L. BROWN, Chicago: I presume that Dr. Verhoeff bases his main identification of this eye on the hyaline transformation of the ciliary body, and in this connection I want to mention an article by Professor Fuchs in which the occurrence of hyaline degeneration in early years is mentioned. I have translated the article and if any of you are interested I will be glad to send you a copy.

DR. F. H. VERHOEFF, closing: The American Ophthalmological Society three years ago, by vote, decided to adopt the term "retinoblastoma" and I feel sure that Dr. Benedict voted in favor of it, yet now he uses the term "neuroblastoma" instead. I should like to know whether he now has a weighty reason that has induced him to abandon the term "retinoblastoma."

DR. WILLIAM L. BENEDICT, closing: At a former meeting of this Society there was an occasion on which a member said that he was neither a pathologist nor the son of a pathologist. I am in exactly the same situation. In the pathologist's report he wrote over his signature that this was a neuroblastoma. I apologize to Dr. Verhoeff and will take this up with the pathologist and see that it is straightened out.

That the lenticular changes are due to radium is to my mind open to question. In the large number of eyes I have observed that have been irradiated because of tumor of the adnexa, I have yet to find a single instance, aside from this one, in which the lens has developed opacities. This child did not develop the lenticular opacity until more than five years after the first application of radium, and during that time characteristic choroidal atrophy had taken place.

I have another case similar to this in a child less than seven years of age, referred by Dr. Meyer Wiener. A similar tumor was found in both eyes. Radium was given with immediate reduction of the size of the tumor. There was a recrudescence of the growth in both

eyes. One was finally lost, but the other recovered. It is only three years, however, since the first application of radium, but to date there are no opacities in the lens of the remaining eye, but there are characteristic atrophic changes in the choroid.*

I have here two photographs which show that the changes are in all particulars similar to the lens changes seen in marked choroidal disturbance which Dr. Weeks told me some time ago they had found in such cases.

TERMINAL STAGE IN A CASE OF RETINITIS WITH MASSIVE EXUDATION †

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AND
JONAS S. FRIEDENWALD, M.D.
Baltimore

Since Coats first directed attention to the curious condition which bears his name, quite a number of cases have been reported. These have for the most part been observed for but short periods, and the interest of the writers has been directed to the ophthalmoscopic picture in the active stages, and to the pathologic changes discovered after enucleation. Little has been added to Coats' statement:‡ "In the later stages detachment of the retina, secondary cataract, iritis, decrease of intra-ocular tension or glaucoma may lead to loss of the eye, but some cases may come to a standstill before such consequences appear." In a paper by one of us read before the American Ophthalmological Society in 1914§ a series of five cases was reported, with pathologic studies of two eyes enucleated, and with colored pictures of two fundi. Of the latter, case 5 illustrated the condition of a young man, then aged seventeen years, which was described as follows:

* Since this report was given this child died of general metastasis without notable increase in the size of the tumor in the remaining eye.

† From the Departments of Ophthalmology of the University of Maryland and the Johns Hopkins University.

‡ Arch. f. Ophth., 1912, lxxxi, p. 275.

§ Tr. Am. Ophth. Soc., 1914, xiii, p. 819.